REMARKS/ARGUMENTS

Status of the Claims

Claims 1-3, 6-12, and 38-47 are pending in the current application. Reexamination and reconsideration are respectfully requested in view of the following remarks.

The Rejections Under 35 U.S.C. § 112, First Paragraph, Should be Withdrawn

Claims 1-3, 6-12, and 38-47 have been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification fails to provide a sufficient written description of the claimed invention. The rejection is respectfully traversed for the reasons described below.

The Examiner argues that the claimed invention lacks an adequate written description because the specification does not provide a representative number of sequences for the proteases whose activities are to be reduced or eliminated or describe the domains required for the function of these protease. Applicants note that the present invention is not directed to the expression of proteases having proteolytic activity. Rather, the present invention is directed to plants that are genetically modified to *reduce* or *eliminate* the activity of one or more proteases selected from α-vacuolar processing enzyme, β-vacuolar processing enzyme, γ-vacuolar processing enzyme, ε-vacuolar processing enzyme, aspartic protease AP1, and aspartic protease AP2. As is well known to those of skill in the art, no knowledge of functional domains is required to reduce or eliminate the expression of an endogenous protein in a plant. For example, reduction of the expression of plant protein may be obtained by the expression of sense, antisense, or hairpin RNAs corresponding to *any* region of the target mRNA. sequence. See, for example, U.S. Patent Nos. 5,283,184, 5,034,323, and 5,942,657 (cited on page 23 of the specification and provided as appendices G, H, and I with Applicants response mailed December 17, 2003), which describe the successful use of antisense suppression and sense suppression to inhibit the expression of endogenous plant genes. See also Stam *et al.* (1997) *Plant J.* 12:63-82, and WO 99/32619 (Fire *et al.*), provided as Appendices A and B with the accompanying

Declaration under Rule 132. These references teach the use of interfering RNAs containing inverted repeat sequences to reduce the expression of an endogenous plant gene.

The Federal Circuit has stated that sufficient written description simply requires that the knowledge and level of skill in the art would permit one of skill in the art to immediately envision the product claimed from the disclosure. *Purdue Pharm L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323; 596 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("One skilled in the art must immediately discern the limitations at issue in the claims."). The present application meets this standard because it describes the claimed invention, i.e. plants that have been genetically modified to reduce or eliminate the activity of one or more proteases selected from α-vacuolar processing enzyme, β-vacuolar processing enzyme, γ-vacuolar processing enzyme, ε-vacuolar processing enzyme, aspartic protease AP1, and aspartic protease AP2, such that one of skill in the art would be able to envision them. Plant vacuolar processing enzymes and aspartic proteases and the domains that characterize them are well known to those of skill in the art as described on pages 2-3 of the specification and the references cited therein, and in Applicants' response mailed December 17, 2003. Accordingly, the requirement for a written description of the claimed invention is satisfied.

The facts of the present case are highly analogous to those in *Amgen Inc. v. Hoechst Marion Roussel, Inc.* 314 F.3d 1313; 57 USPQ2d (Fed. Cir. 2003). One of the issues before the court in *Amgen* was whether Amgen's claims directed to cells capable of producing erythropoietin, where the cells comprised non-human DNA sequences that controlled the transcription of a DNA encoding human erythropoietin, met the written description requirement. One of the accused infringers of the claims, Transkaroytic Technologies (TKT), argued that Amgen had failed to sufficiently describe all of the cells as engineered in the claimed invention. TKT cited *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Gen-Probe,* nc. I296 F.3d 1315, 63 USPQ2d 1609 (Fed. Cir. 2002) in support of this argument. The Federal Circuit disagreed, finding that Agmen's claims were distinguishable from the claims of both of these cases. The court stated:

> Both *Eli Lilly* and *Enzo Biochem* are inapposite to this case because the claim terms at issue are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend. Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO. Thus, TKT can only challenge the adequacy of disclosure of the vertebrate or mammalian host cell—not the human DNA itself.

Amgen, 314 F.3d at 1333, 57 USPQ2d at 1507.

Similarly, the claim terms at issue in the present application are not new or unknown biological materials that ordinary skilled artisans would easily miscomprehend. Rather, they are directed to classes of plant proteases that were known to those of skill in the art as of the filing date of the present application. Examples of *Arabidopsis* vacuolar processing enzymes and aspartic proteases are described in the specification on lines 4-13 of page 7. The domains of these proteins that are important for their proteolytic activity are known in the art as described in Applicants response mailed December 17, 2003. In addition, the amino acid sequence of vacuolar processing enzymes and aspartic protease from various plants were known in the art at the time the present application was filed. See, for example, the references cited in pages 2-3 and 7 of the specification, and the Pfam alignments provided as Appendices A-C, E, and F with Applicants' response mailed December 17, 2003. Accordingly, one of skill in the art would be able to recognize members of these protease families.

In summary, based on the evidence described above, claims 1-3, 6-12, and 38-47 meet the written description requirement because one of skill in the art could immediately envision the claimed genetically-modified plant from the disclosure, and would therefore recognize that the Applicants were in possession of the claimed invention at the time the application was filed. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph for insufficient written description should be withdrawn.

Claims 1-3, 6-12, and 38-47 have further been rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification does not provide sufficient guidance to enable a person of skill in the art to make and use the invention. The rejection is respectfully traversed for the reasons described below.

In the Office Action mailed July 17, 2003, the Examined cited Bryant *et al.* to demonstrate that different plant lines transformed with an antisense construct targeting chalcone synthase showed varying levels of gene suppression. In Applicants' response mailed December 17, 2003, Applicants showed that Bryant *et al.* were able to obtain plants in which chalcone synthase expression was substantially suppressed, and that the authors indicate that such plants could be obtained merely by screening a population of transformed plants to identify those plants showing the highest level of gene silencing. Nevertheless, the Examiner has maintained the rejection on the basis of Bryant *et al.* on the grounds that the reference demonstrates that unpredictable results are obtained with antisense technology.

The arguments set forth in the Office action suggest that that because not all transformations with antisense constructs will result in a significant level of gene silencing, it would require undue experimentation to identify those plants having reduced protease activity. However, the standard set forth in the office action is not supported by the applicable case law. The fact that not every transgenic plant produced by transformation with a gene silencing vector will show significant levels of gene silencing does not necessarily mean that undue experimentation is required to make such a plant. For example, in *Ex parte Chen*, 61 USPQ2d 1025 (B.P.A.I. Aug. 22, 2001), the Board of Patent Appeals and Interferences addressed the issue of whether claims directed to transgenic carp lacked enablement. The Examiner had argued that the low success rate (1 % or 20 out of 1746 attempts) of obtaining carp embryos with integrated transgenes indicated that undue experimentation was required to practice the invention. However, the Board disagreed, stating:

> [T]he examiner offers no evidence which would reasonably support a conclusion that one skilled in this art would regard this rate of success for the integration of the rtGH gene as evidencing undue experimentation. We remind the examiner that some experimentation may be required as long as it is not undue . . .As the record now stands, the numbers emphasized by the examiner would reasonably appear to reflect the need for a repetitive procedure, rather than undue experimentation by those wishing to practice the invention.

Id. at 1028.

Similarly, in the present case there is no evidence that one of skill in the art would consider the optimization required to genetically modify a plant to reduce the activity of one or

more proteases to be undue experimentation. Rather, as described in Applicants' response mailed December 17, 2003, the evidence of record, including the art cited by the Examiner, shows that a number of methods for reducing the expression of endogenous plant genes were known in the art at the time the present application was filed, that these methods had been used to reduce or eliminate the activity of a number of plant genes, and that those in the art viewed these methods as a viable tool in elucidating gene function and in creating genetically engineered plants.

Furthermore, the present invention is directed to plants that have been genetically modified to reduce or eliminate the activity of one or more plant proteases, and is not tied to a particular method or producing the claimed plants. The Federal Circuit has held "[t]he enablement requirement is met if the description enables *any* mode of making and using the claimed invention." *Engel Industries Inc. v. The Lockformer Co.*, 20 USPQ2d 1300, 1304 (Fed. Cir. 1991), emphasis added. The present invention clearly satisfies this requirement, because it provides working examples of plants that are genetically modified to reduce the activity of β-VPE and ϵ-VPE. Accordingly, there is no *prima facie* showing that the claimed invention is not enabled.

In addition, the Applicants have performed experiments in which the methods disclosed in the present application were used to produce plants that were genetically modified to reduce or eliminate the activity of plant vacuolar processing enzymes and/or aspartic proteases. These experiments are described in detail in the accompanying Rule 132 declaration of Dr. Rudolf Jung.

The declaration describes the use of gene silencing by hairpin RNA interference to produce transgenic *Arabidopsis* lines having reduced activity for three aspartic proteases. To produce these plants, a gene silencing vector containing sense fragments of three *Arabidopsis* aspartic protease coding sequences (the AP 1-2-3 RNAi vector) was transformed into an *Arabidopsis* mutant background that has knock-out insertions in four vacuolar processing enzyme genes (the "vpe-quad mutant"; see Gruis *et al.* (2004) *Plant Cell* 16:270-90). The gene silencing vector contained an inverted repeat of a sequence corresponding to fragments of the *Arabidopsis* aspartic protease coding sequences set forth in set forth in NCBI Accession Nos.

NM_104909, NM_101062, and NM_116684. This vector was designed according to the teachings of Stam *et al.* (1997) *Plant J.* 12:63-82, and WO 99/32619 (Fire *et al.*), published July 1, 1999. Seed from the transformed plants showed a marked reduction in the processing of the seed storage protein albumin in comparison with control plants that did not contain the silencing cassettes, demonstrating that the activity of the aspartic proteases was reduced in the seed of these plants. Accordingly, the experiment demonstrates the successful production of genetically modified *Arabidopsis* plants having reduced activity for four VPE's as well as for three aspartic proteases using gene silencing techniques that were known to those of skill in the art at the time the present application was filed.

The declaration also describes a second experiment in which genetically modified soybean lines having reduced activity for five different vacuolar processing enzymes were produced. These transgenic soybean lines were produced by transforming soybean with a gene silencing vector, KS217, containing an inverted repeat of a nucleic acid molecule comprising sequences corresponding to fragments of the mRNAs of five soybean vacuolar processing enzymes. Two of the soybean VPE's targeted by this silencing construct, VPE1 and VPE1b, are set forth in NCBI Accession Nos. D28876 and AF169019, respectively. The other three soybean VPE's, VPE2, VPE2b, and VPE3, are set forth as SEQ ID NOS:5, 7, and 9 of U.S. Provisional Patent Application No. 60/529,666 filed December 15, 2003, a copy of which has been provided as Appendix C of the accompanying Rule 132 Declaration. U.S. Patent Application No. 60/529,666 is directed to soybean plants that are genetically modified to alter the functional properties of seed storage proteins. This patent application discloses the soybean VPE2, VPE2b, and VPE3 sequences and teaches that the functional properties of soybean proteins may be altered by reducing the activity of these proteases.

This soybean VPE silencing cassette was designed according to the teachings of Stam *et al.* (1997) *Plant J.* 12:63-82, and WO 99/32619 (Fire *et al.*). Seed from the transformed plants showed a marked accumulation in pro-glycinin, the precursor for the seed storage protein glycinin. This alteration in seed storage protein processing demonstrates that the activity of the vacuolar processing enzymes was reduced in the seed of these genetically modified plants.

Accordingly, the Rule 132 Declaration of Dr. Rudolf Jung demonstrates that one of skill in the art one of skill in the art, relying on the present disclosure and on the knowledge in the art at the time the present application was filed, would be able to produce a plant that is genetically modified to reduce the activity of vacuolar processing enzymes and aspartic proteases. Furthermore, the experiments described in the declaration demonstrate the reduction of activity of aspartic protease and vacuolar processing enzymes from *Arabidopsis* and soybean that were identified after the filing date of the present application. Accordingly, the declaration demonstrates that the methods of the invention are enabled for reducing the activity of later-identified proteases.

In view of the above arguments, all grounds for rejection under 35 U.S.C. § 112, first paragraph, have been overcome. Accordingly, reconsideration and withdrawal of the rejections are respectfully requested.

CONCLUSION

It is believed that the pending claims are patentable over the cited references. Early notice to this effect is solicited. If in the opinion of the Examiner an interview would expedite prosecution, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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